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(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SHAH, Shrenik, K. [IN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). GRANT, Stephan, K. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MACCOSS, Malcolm [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SHANKARAN, Kothandaraman [IN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). QI, Hongbo [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). GUTHIKONDA, Ravindra, N. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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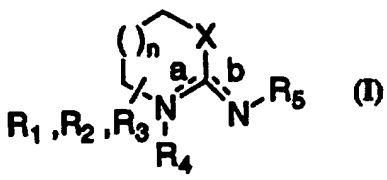
(54) Title: SUBSTITUTED HETEROCYCLES AS INHIBITORS OF NITRIC OXIDE SYNTHASE

(57) Abstract



(I)

Disclosed herein are compounds of Formula (I) and pharmaceutically acceptable salts thereof which have been found useful in the treatment of nitric oxide synthase mediated diseases and disorders, including neurodegenerative disorders, disorders of gastrointestinal motility and inflammation. Theses diseases and disorders include hypotension, septic shock, toxic shock syndrome, hemodialysis, IL-2 therapy such as in cancer patients, cachexia, immunosuppression such as in transplant therapy, autoimmune and/or inflammatory indications including sunburn or psoriasis and respiratory conditions such as bronchitis, asthma, and acute respiratory distress (ARDS), myocarditis, heart failure, atherosclerosis, arthritis, rheumatoid arthritis, chronic or inflammatory bowel disease, ulcerative colitis, systemic lupus erythematosis (SLE), ocular conditions such as ocular hypertension and uveitis, type 1 diabetes, insulin-dependent diabetes mellitus and cystic fibrosis. Compounds of Formula (I) are also useful in the treatment of hypoxia, hyperbaric oxygen convulsions and toxicity, dementia, Sydenham's chorea, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, Korsakoff's disease, imbecility related to cerebral vessel disorder, ischemic brain edema, sleeping disorders, schizophrenia, depression, PMS, anxiety, drug addiction, pain, migraine, immune complex disease, as immunosupressive agents and for preventing or reversing tolerance to opiates and diazepines.

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TITLE OF THE INVENTION

SUBSTITUTED HETEROCYCLES AS INHIBITORS OF NITRIC OXIDE SYNTHASE

BACKGROUND OF THE INVENTION

This application is directed to inhibitors of Nitric oxide synthase, and in particular thiazolines and thiazines.

Nitric Oxide in Biology.

The emergence of nitric oxide (NO), a reactive, inorganic radical gas as a molecule contributing to important physiological and pathological processes is one of the major biological revelations of recent times. This molecule is produced under a variety of physiological and pathological conditions by cells mediating vital biological functions. Examples include endothelial cells lining the blood vessels; nitric oxide derived from these cells relaxes smooth muscle and regulates blood pressure and has significant effects on the function of circulating blood cells such as platelets and neutrophils as well as on smooth muscle, both of the blood vessels and also of other organs such as the airways. In the brain and elsewhere nitric oxide serves as a neurotransmitter in non-adrenergic non-cholinergic neurons. In these instances nitric oxide appears to be produced in small amounts on an intermittent basis in response to various endogenous molecular signals. In the immune system nitric oxide can be synthesized in much larger amounts on a protracted basis. Its production is induced by exogenous or endogenous inflammatory stimuli, notably endotoxin and cytokines elaborated by cells of the host defense system in response to infectious and inflammatory stimuli. This induced production results in prolonged nitric oxide release which contributes both to host defense processes such as the killing of bacteria and viruses as well as pathology associated with acute and chronic inflammation in a wide variety of diseases. The discovery that nitric oxide production is mediated by a unique series of three closely related enzymes, named nitric oxide synthases, which utilize

the amino acid arginine and molecular oxygen as co-substrates has provided an understanding of the biochemistry of this molecule and provides distinct pharmacological targets for the inhibition of the synthesis of this mediator, which should provide significant beneficial effects in a wide variety of diseases.

Nitric Oxide Synthases

Nitric oxide and L-citrulline are formed from L-arginine via the dioxygenase activity of specific nitric oxide synthases (NOSs) in mammalian cells. In this reaction, L-arginine, O_2 and NADPH are cosubstrates while FMN, FAD and tetrahydrobiopterin are cofactors. NOSs fall into two distinct classes, constitutive NOS (cNOS) and inducible NOS (iNOS) . Two constitutive NOSs have been identified. They are:

(i) a constitutive, Ca^{++}/calmodulin dependent enzyme, located in the endothelium (ecNOS or NOS 3), that releases NO in response to receptor or physical stimulation,

(ii) a constitutive, Ca^{++}/calmodulin dependent enzyme, located in the brain (ncNOS or NOS 1) and elsewhere, that releases NO in response to receptor or physical stimulation,

The third isoform identified is inducible NOS (iNOS or NOS 2):

(iii) a Ca^{++} independent enzyme which is induced after activation of vascular smooth muscle, macrophages, endothelial cells, and a large number of other cells by endotoxin and cytokines. Once expressed, this inducible NO synthase produces NO in relatively large amounts for long periods of time.

Spectral studies of both the mouse macrophage iNOS and rat brain ncNOS have shown that these enzymes (which has been classified as P-450-like from their CO-difference spectra) contain a heme moiety. The structural similarity between NOS and the P-450/flavoprotein

complex suggests that the NOS reaction mechanism may be similar to P-450 hydroxylation and/or peroxidation. This indicates that NOS belongs to a class of flavohemeproteins which contain both heme and flavin binding regions within a single protein in contrast to the multiprotein NADPH oxidase or Cytochrome P-450/NADPH Cyt c reductase complexes.

Distinct Functions of NO Produced by Different Nitric Oxide Synthases.

The NO released by the constitutive enzymes (NOS 1 and NOS 3) acts as an autocoid mediating a number of physiological responses. Two distinct cDNAs accounting for the activity of NOS 1 and NOS 3 in man have been cloned, one for NOS 1 (Nakane *et. al., FEBS Letters, 316*, 175-182, 1993) which is present in the brain and a number of peripheral tissues, the other for an enzyme present in endothelium (NOS 3) (Marsden *et. al., FEBS Letters, 307*, 287-293, 1992). This latter enzyme is critical for production of NO to maintain vasorelaxation. A second class of enzyme, iNOS or NOS 2, has been cloned from human liver (Geller *et. al., PNAS, 90*, 3491-5, 1993), and identified in more than a dozen other cells and tissues, including smooth muscle cells, chondrocytes, the kidney and airways. As with its counterpart from the murine macrophage, this enzyme is induced upon exposure to cytokines such as gamma interferon (IFN-γ), interleukin-1β (IL-1β), tumor necrosis factor (TNF-α) and LPS (lipopolysaccharide). Once induced, iNOS expression continues over a prolonged period of time. The enzyme does not require exogenous calmodulin for activity.

Endothelium derived relaxation factor (EDRF) has been shown to be produced by NOS 3 (Moncada *et. al., Pharmacol. Reviews, 43*, 109-142, 1991). Studies with substrate analog inhibitors of NOS have shown a role for NO in regulating blood pressure in animals and blood flow in man, a function attributed to NOS 3. NO has also been shown to be an effector of the cytotoxic effects of activated macrophages (Nathan, *FASEB J., 6*, 3051-64, 1992) for fighting tumour cells and invading microorganisms (Wright *et al., Card. Res., 26* ,48-57, 1992 and

Moncada *et al.*, *Pharmacological Review*, *43*, 109-142, 1991). It also appears that the adverse effects of excess NO production, in particular pathological vasodilation and tissue damage, may result largely from the effects of NO synthesized by the NOS 2.

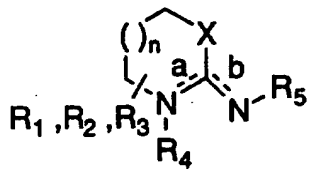
NO generated by NOS 2 has been implicated in the pathogenesis of inflammatory diseases. In experimental animals hypotension induced by LPS or TNF-α can be reversed by NOS inhibitors and reinitiated by L-arginine (Kilbourn *et. al.*, *PNAS*, *87*, 3629-32, 1990). Conditions which lead to cytokine-induced hypotension include septic shock, hemodialysis (Beasley and Brenner, *Kidney Int.*, *42*, Suppl., *38*, S96--S100, 1992) and IL-2 therapy in cancer patients (Hibbs *et. al.*, *J. Clin. Invest.*, *89*, 867-77, 1992). NOS 2 is implicated in these responses, and thus the possibility exists that a NOS inhibitor would be effective in ameliorating cytokine-induced hypotension. Recent studies in animal models have suggested a role for NO in the pathogenesis of inflammation and pain and NOS inhibitors have been shown to have beneficial effects on some aspects of the inflammation and tissue changes seen in models of inflammatory bowel disease, (Miller *et. al.*, *J. Pharmacol. Exp. Ther.*, *264*, 11-16, 1990) and cerebral ischemia and arthritis (Ialenti *et. al.*, *Br. J. Pharmacol.*, *110*, 701-6, 1993; Stevanovic-Racic *et al.*, *Arth. & Rheum.*, *37*, 1062-9, 1994). Moreover transgenic mice deficient in NOS 1 show diminished cerebral ischemia (Huang *et. al.*, *Science*, *265*, 1883-5, 1994).

Further conditions where there is an advantage in inhibiting NO production from L-arginine include therapy with cytokines such as TNF, IL-1 and IL-2 or therapy with cytokine-inducing agents, for example 5, 6-dimethylxanthenone acetic acid, and as an adjuvant to short term immunosuppression in transplant therapy. In addition, compounds which inhibit NO synthesis may be of use in reducing the NO concentration in patients suffering from inflammatory conditions in which an excess of NO contributes to the pathophysiology of the condition, for example adult respiratory distress syndrome (ARDS) and myocarditis.

There is also evidence that an NO synthase enzyme may be involved in the degeneration of cartilage which takes place in autoimmune and/or inflammatory conditions such as arthritis, rheumatoid arthritis, chronic bowel disease and systemic lupus erythematosis (SLE). It is also thought that an NO synthase enzyme may be involved in insulin- dependent diabetes mellitus. Therefore, a yet further aspect of the present invention provides thiazine and thiazolone derivatives or salts thereof in the manufacture of a medicament for use in cytokine or cytokine-inducing therapy, as an adjuvant to short term immunosuppression in transplant therapy, for the treatment of patients suffering from inflammatory conditions in which an excess of NO contributes to the pathophysiology of the condition.

SUMMARY OF THE INVENTION

The invention disclosed herein encompasses compounds of Formula I



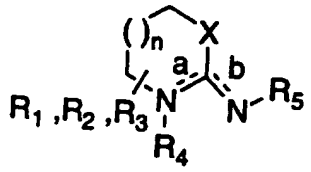
I

and pharmaceutically acceptable salts thereof which have been found useful in the treatment of nitric oxide synthase mediated diseases and disorders, including neurodegenerative disorders, disorders of gastrointestinal motility and inflammation. These diseases and disorders include hypotension, septic shock, toxic shock syndrome, hemodialysis, IL-2 therapy such as in in cancer patients, cachexia, immunosuppression such as in transplant therapy, autoimmune and/or inflammatory indications including sunburn, eczema or psoriasis and respiratory conditions such as bronchitis, asthma, oxidant-induced lung injury and acute respiratory distress (ARDS), glomerulonephritis, inflammatory

sequelae of viral infections, myocarditis, heart failure, atherosclerosis, arthritis, rheumatoid arthritis, chronic or inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosis (SLE), ocular conditions such as ocular hypertension, retinitis and uveitis, type 1 diabetes, insulin-dependent diabetes mellitus and cystic fibrosis. Compounds of Formula I are also usful in the treatment of hypoxia, hyperbaric oxygen convulsions and toxicity, dementia, Sydenham's chorea, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, mulitple sclerosis, Korsakoff's disease, imbecility related to cerebral vessel disorder, NO mediated cerebral trauma and related sequelae, ischemic brain edema, sleeping disorders, schizophrenia, depression, pre-menstrual syndrome (PMS), anxiety, drug addiction, pain, migraine, immune complex disease, as immunosupressive agents, acute allograft rejection, infections caused by invasive microorganisms which produce NO and for preventing or reversing tolerance to opiates and diazepines.

DETAILED DESCRIPTION OF THE INVENTION

The invention disclosed herein encompasses compounds of Formula I



I

and pharmaceutically acceptable salts thereof wherein
side a or side b has a double bond,
n is 0, 1, 2, 3 or 4
X is selected from C_2, O, S and NH,
R_1, R_2 and R_3 are each independently selected from the group consisting of

(a) hydrogen,

(b) C_{1-12}alkoxy,
(c) C_{1-12}alkylS(O)$_k$ wherein k is 0, 1 or 2,
(d) mono C_{1-12}alkylamino,
(e) (di-C_{1-12}alkyl)amino,
(f) C_{1-12}alkylcarbonyl,
(g) C_{1-12}alkyl,
(h) C_{2-12}alkenyl,
(i) C_{2-12}alkynyl,
(j) C_{5-10}cycloalkyl,
(k) hetero C_{5-10}cycloalkyl,wherein the hetero C_{5-10}cycloalkyl optionally contains 1 or 2 heteroatoms selected from S, O and N,
(l) aryl, selected from phenyl or naphthyl,
(m) heteroaryl, wherein heteroaryl is selected from the group consisting of:
(1) benzimidazolyl,
(2) benzofuranyl,
(3) benzooxazolyl,
(4) furanyl,
(5) imidazolyl,
(6) indolyl,
(7) isooxazolyl,
(8) isothiazolyl,
(9) oxadiazolyl,
(10) oxazolyl,
(11) pyrazinyl,
(12) pyrazolyl,
(13) pyridyl,
(14) pyrimidyl,
(15) pyrrolyl,
(17) isoquinolyl,
(18) tetrazolyl,
(19) thiadiazolyl,
(20) thiazolyl,

(21) thienyl, and
(22) triazolyl,

(n) amino,
(o) oxo,
(p) C(O)OH,
(q) $C(O)OR_6$, R_6 is selected from hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl,

each of (b) to (m) being optionally mono or di- substituted the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$, where R_7 is selected from hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl,
(4) $-OR_6$,
(5) $-CO2R_6$,
(6) $-S(O)_kR_6$,
(7) halo selected from F, Cl, Br and I,
(8) $-C(=NR_6)-NHR_7$,
(9)-S-$C(=NR_6)-NHR_7$,

provided that when R_1, R_2 or R_3 is hydroxy, amino, mono C_{1-4}alkylamino or (di-C_{1-4}alkyl)amino, said R_1, R_2 or R_3 must not reside alpha to a hetero atom of the ring on which it resides,

or when two members of the group R_1, R_2 and R_3 reside on the same carbon atom of Formula I, or two of the group R_1, R_2 and R_3 reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the carbon atom to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R_1, R_2 and R_3 resides on an atom adjacent to the N on which R_4 resides, said member may optionally be joined with R_4, such that together with the N

on which R4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

R4 and R5 are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C1-12alkyl, optionally mono or di-substituted, the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) -NR6R7,
(4) -OR6,
(5) -CO2R6,
(6) -S(O)kR6,
(7) halo selected from F, Cl, Br and I,
(8) phenyl, optionally mono or di-substituted with hydroxy, halo, C1-4alkyl, or C1-4alkoxy,

(c) -CONR8R9, where R8 and R9 are each independently hydrogen, phenyl, cyclohexyl or C1-6alkyl, said C1-6alkyl optionally substituted by

(1) hydroxy,
(2) amino,
(3) carboxy,
(4) -NR10R11, wherein R10 and R11 are each independently H, C1-6alkyl, phenyl or benzyl,
(5) -OR10,
(6) -CO2R10,
(7) -S(O)mR10, where m is 0, 1 or 2,
(8) halo selected from F, Cl, Br and I,
(9) optionally substituted aryl wherein aryl and aryl substituents are as defined above,

(10) optionally substituted heteroaryl wherein heteroaryl and heteroaryl substituents are as defined above,

(11) optionally substituted C5-10cycloalkyl wherein cycloalkyl and cycloalkyl substituents are as defined above,

(12) optionally substituted hetero C5-10cycloalkyl wherein hetero cycloalkyl and hetero cycloalkyl substituents are as defined above,

(d) -CSNR8R9,

(e) -COR9,

(f) -CO2R9,

(g) -CSR9,

(h) phenyl,

(i) cyclohexyl,

provided that R4 is present only when side a is a single bond and side b is a double bond, and further provided that when n is 0 or 1, X is S and R1, R2, R3, and R4 are hydrogen, then R5 is other than hydrogen or methyl.

Within this embodiment is the genus wherein

n is 0, 1, 2, 3 or 4

X is selected from O, S and NH,

R1, R2 and R3 are each independently selected from the group consisting of

(a) hydrogen,

(b) C1-6alkoxy,

(c) C1-6alkylamino,

(d) C1-6alkylcarbonyl,

(e) C1-6alkyl,

(f) C2-6alkenyl,

(g) C5, C6 or C7cycloalkyl,

(h) hetero C5 or C6 cycloalkyl,wherein the hetero C5 or C6 cycloalkyl optionally contains 1 heteroatom selected from S, O and N,

(i) aryl, selected from phenyl or naphthyl,

(j) heteroaryl, wherein heteroaryl is selected from the group consisting of:

(1) furanyl,
(2) pyrazinyl,
(3) pyrazolyl,
(4) pyridyl,
(5) pyrimidyl,
(6) thiazolyl,
(7) thienyl, and
(8) triazolyl,

each of (b) to (j) being optionally mono or di- substituted the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) -NR_6R_7, where R_6 and R_7 are each independently hydrogen, phenyl or C_{1-4}alkyl,
(4) -OR_6,
(5) -CO_2R_6,
(6) -$S(O)_kR_6$, where k is 0, 1 or 2,
(7) halo selected from F, Cl, Br and I,
(8) -$C(=NR_6)$-NHR_7,
(9)-S-$C(=NR_6)$-NHR_7,

or when two members of the group R_1, R_2 and R_3 reside on the same carbon atom of Formula I, or two of the group R_1, R_2 and R_3 reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the carbon atom to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R_1, R_2 and R_3 resides on an atom adjacent to the N on which R_4 resides, said member may optionally be joined with R_4, such that together with the N on which R_4 resides and the carbon on which said member

resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

R4 and R5 are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-6}alkyl, optionally mono or di-substituted, the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$,
(4) $-OR_6$,
(5) $-CO2R_6$,
(6) $-S(O)_kR_6$, where k is 0, 1 or 2,
(7) halo selected from F, Cl, Br and I,

(c) $-CONR_8R_9$, where R_8 and R_9 are each independently hydrogen, phenyl, cyclohexyl or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by

(1) hydroxy,
(2) amino,
(3) carboxy,
(4) $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently H, C_{1-4}alkyl, phenyl or benzyl,
(5) $-OR_{10}$,
(6) $-CO2R_{10}$,
(7) $-S(O)_mR_{10}$, where m is 0, 1 or 2,
(8) halo selected from F, Cl, Br and I,
(9 optionally substituted aryl wherein the aryl and substituents are as defined above,
(10) optionally substituted heteroaryl wherein the heteroaryl and substituents are as defined above,
(11) optionally substituted C_5 or C_6 cycloalkyl wherein the cycloalkyl and substituents are as defined above,

(12) optionally substituted hetero C_5 or C_6 cycloalkyl wherein the hetero cycloalkyl and substituents are as defined above,

(d) -CSNR8R9,

(e) -COR9,

(f) -CO_2R9,

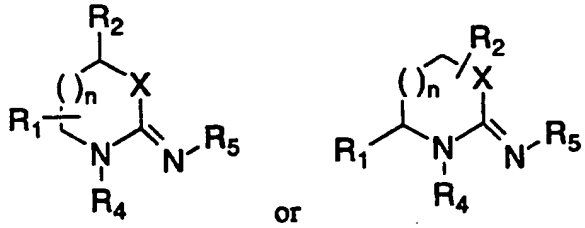
(g) -CSR9,

(h) phenyl,

(i) cyclohexyl,

such that R4 is present only when side a is a single bond and side b is a double bond.

Within this genus is the class of compounds of the formulae Ia and Ib or tautomers thereof



Ia or Ib

wherein

n is 0, 1 or 2

X is selected from O, S and NH,

R_1 and R_2 are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-4}alkyl, said C_{1-4}alkyl being optionally mono or di- substituted the substituents being independently selected from

(1) carboxy,

(2) -NHR7, wherein R6 and R7 are each independently hydrogen or C_{1-3}alkyl,

(3) -OR6,

(4) -CO2R6,

(5) -S(O)kR6, where k is 0, 1 or 2,

R4 is selected from the group consisting of

(a) hydrogen,

(b) -CONHR9, where R9 is hydrogen or C1-3alkyl, said C1-3alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) -NR10R11, wherein R10 and R11 are each independently C1-3alkyl,

(5) -OR10,

(6) -CO2R10,

(7) -S(O)mR10, where m is 0, 1 or 2,

(9) halo selected from F, Cl, Br and I,

(c) -CSNHR9;

(d) C1-3alkyl;

R5 is selected from the group consisting of

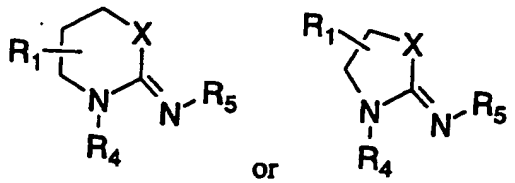
(a) hydrogen,

(b) -CONHR9,

(c) -CSNR8R9.

(d) C1-3alkyl.

Within this class are the compounds of the formulae



and tautomers thereof.

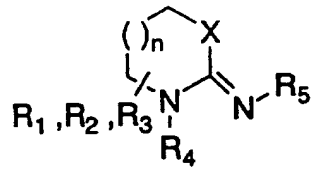
Illustrating the invention are Examples 1 through 41 disclosed hereinunder.

As appreciated by those of skill in the art the additional carbon members of the Formula I ring, "( )n" and definitions "CH2" and

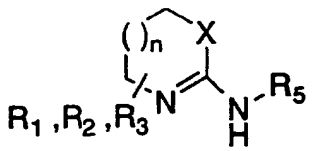
"NH" under X, provide available positions for the substituents R_1, R_2 or R_3.

When any variable (e.g. R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, Ra, Rb, k, n, p etc.) occurs in any position of a compound of Formula I, it's definition on each occurrence is independent of it's definition at every occurrence.

As appreciated by those of skill in the art, compounds of Formula I include those wherein there is a double bond at side a or b such as shown in Ia and Ib or tautomeric forms thereof

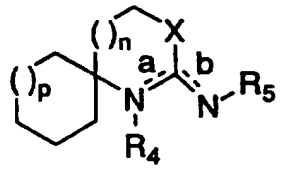


Ia

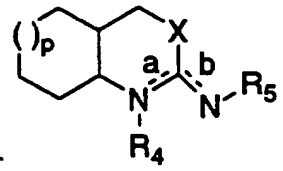


Ib

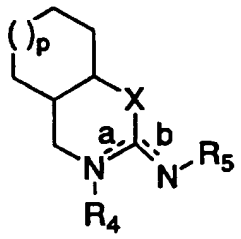
As also appreciated by those of skill in the art, compounds of Formula 1 wherein or when two members of the group R_1, R_2 and R_3 are joined together to form a ring are intended to include such formulae as:



or

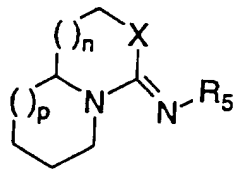


or



wherein p is 0, 1, or 2 and n is defined as above and wherein the second ring may contain up to three hetero atoms selected from N, O or S

Similarly, compounds of Formula I wherein a member of the group R_1, R_2 and R_3 resides on an atom adjacent to the N on which R_4 resides and forms a ring therewith may be illustrated by:



wherein p is 0, 1, or 2 and wherein the second ring may contain up to three hetero atoms selected from N, O or S

For purposes of this specification alkyl is defined to include linear, branched, and cyclic structures, with C1-6alkyl including methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Similarly, C1-6alkoxy is intended to include alkoxy groups of from 1 to 6 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. Likewise, C1-6 alkylthio is intended to include alkylthio groups of from 1 to 6 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies $-SCH_2CH_2CH_3$.

Heteroaryl includes furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,3-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3,4-triazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, and the like.

As outlined in the summary of the invention, the compounds of the instant invention are useful for in the treatment of a number of NOS implicated diseases. The implication of these diseases is well documented in the literature. For example, with regard to psoriasis, see Ruzicka *et. al.*, J. Invest. Derm., *103*: 397 (1994) or Kolb-Bachofen *et. al.*, Lancet, *344:* 139 (1994) or Bull, et al., *J. Invest. Derm.*, 103:435(1994); with regard to uveitis, see Mandia *et. al.*, Invest Opthalmol., *35*: 3673-89 (1994); with regard to type 1 diabetes, see Eisieik & Leijersfam, Diabetes & Metabolism, *20*: 116-22 (1994) or Kroncke *et. al.*, *BBRC, 175:* 752-8 (1991) or Welsh *et. al.*, *Endocrinol.*,

129: 3167-73 (1991); with regard to septic shock, see Petros *et. al.*, Lancet, *338*: 1557-8 (1991),Thiemermann & Vane, Eur. J. Pharmacol., *211*: 172-82 (1992), or Evans *et. al.*, Infec. Imm., *60:* 4133-9 (1992), or Schilling *et. al.*, Intensive Care Med., *19:* 227-231 (1993); with regards to pain, see Moore *et. al.*, Brit. J. Pharmacol., *102*: 198-202 (1991), or Moore *et. al*, Brit. J. Pharmacol., *108*: 296-97 (1992) or Meller *et. al.*, *Europ. J. Pharmacol., 214:* 93-6 (1992) or Lee *et. al., NeuroReport, 3:* 841-4 (1992); with regard to migraine, see Olesen *et. al.*, TIPS, *15:* 149-153 (1994); with regard to rheumatoid arthritis, see Kaurs & Halliwell, FEBS Letters, *350:* 9-12 (1994); with regard to osteoarthritis, see Stadler *et. al., J. Immunol., 147:* 3915-20 (1991); with regard to inflammatory bowel disease, see Miller *et. al.*, Lancet, *34*: 465-66 (1993) or Miller *et. al.*, J. Pharmacol. Exp. Ther., *264*: 11-16 (1993); with regard to asthma, see Hamid *et. al.*, Lancet, *342:* 1510-13 (1993) or Kharitonov, *et. al.*, Lancet, *343:* 133-5 (1994); with regard to Immune complex diseases, see Mulligan *et. al.*, Br. J. Pharmacol., *107*: 1159-62 (1992); with regard to multiple sclerosis, see Koprowski *et. al., PNAS, 90:* 3024-7 (1993); with regard to ischemic brain edema, see Nagafuji *et. al.*, Neurosci., *147*: 159-62 (1992) or Buisson *et. al.*, Br. J. Pharmacol., *106*: 766-67 (1992) or Trifiletti *et. al., Europ. J. Pharmacol., 218:* 197-8 (1992); with regard to toxic shock syndrome, see Zembowicz & Vane, PNAS, *89:* 2051-55 (1992); with regard to heart failure, see Winlaw *et. al.*, Lancet, *344:* 373-4 (1994); with regard to ulcerative colitis, see Boughton-Smith *et. al.*, Lancet *342:* 338-40 (1993); and with regard to atherosclerosis, see White *et. al.*, PNAS, *91:* 1044-8 (1994); with regard to glomerulonephritis, see Mühl *et. al., Br. J. Pharmcol., 112:* 1-8 (1994); with regard to paget's disease and osteoporosis, see Löwick *et. al., J. Clin. Invest., 93:* 1465-72 (1994); with regard to inflammatory sequelae of viral infections, see Koprowski *et. al., PNAS, 90:* 3024-7 (1993); with regard to retinitis, see Goureau *et. al., BBRC, 186:* 854-9 (1992); with regard to oxidant induced lung injury, see Berisha *et. al., PNAS, 91:* 744-9 (1994); with regard to eczema, see Ruzica, et al., *J. Invest. Derm.*, 103:395(1994); with regard to acute allograft rejection, see Devlin, J. et al., *Transplantation*, 58:592-595 (1994); and with regard to infection caused by invasive

microorganisms which produce NO, see Chen, Y and Rosazza, J.P.N., *Biochem. Biophys. Res. Comm.*, 203:1251-1258(1994).

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethyl-cellulose, methylcellulose, hydroxy-propylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy beans, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed.

(For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day, preferably 2.5 mg to 1 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Assay Protocol for NOS activity

NOS activity is measured as the formation of L-[2,3,4,5-^{3}H]Citrulline from L-[2,3,4,5-^{3}H]Arginine. The incubation buffer (100 µL) contained; 100 mM TES, pH 7.5, 5 µM FAD, 5 µM FMN, 10 µM BH_4, 0.5 mM NADPH, 0.5 mM DTT, 0.5 mg/mL BSA, 2 mM $CaCl_2$, 10 µg/mL calmodulin (bovine), 1 µM L-Arg, 0.2 µCi L-[2,3,4,5-^{3}H]Arg, and the inhibitor in aqueous DMSO (max. 5 %). The reaction is initiated by addition of enzyme. Incubations are performed at room temperature

for 30 minutes and stopped by the addition of an equal volume of quenching buffer consisting of 200 mM sodium citrate, pH 2.2, 0.02% sodium azide. Reaction products are separated by passing through a cation exchange resin and quantitated as cpm by scintillation counting. Percent inhibition is calculated relative to enzyme incubated without inhibitor according to: % inhibition = 100 x (cpm L-[2,3,4,5-^{3}H]Cit with inhibitor / cpm L-[2,3,4,5-^{3}H]Cit without inhibitor).

Illustrative of the utility of the compounds of Formula I is the ability of such compounds to inhibit NO synthase as shown in Tables 1-6 and as measured by the assay described above:

TABLE 1

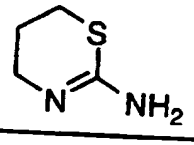
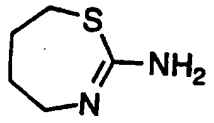
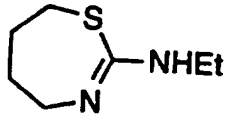
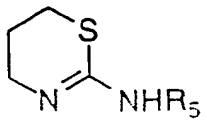
Compound	% inhibition (50uM)
	100
	27.0
	

TABLE 2



R_5	% inhibition (50uM)
H	100
n-Pr	78

TABLE 3

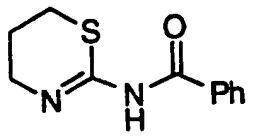
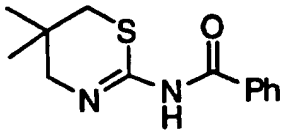
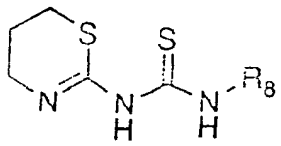
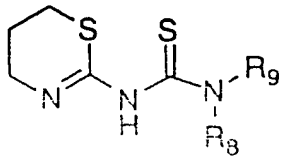
Compound	% inhibition (50uM)
	79
	65

TABLE 4



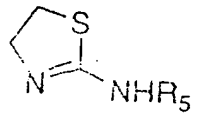
R8	% inhibition (50uM)
Me	85
Et	86
n-Pr	57
i-Pr	91
n-Bu	96
cyclohexyl	83
phenyl	89

TABLE 5



R8	R9	% inhibition (50uM)
$CH_2CH_2NMe_2$	H	81
$CH_2CH_2CH_2NMe_2$	H	94
$CH_2CH_2CH_2NEt_2$	H	58
$CH_2CH_2NMe_2$	Et	50
$CH_2CH_2NEt_2$	Et	69
$CH_2CH_2NMe_2$	CH_2-Ph	80
$CH_2CH_2N(Me)CH_2Ph$	Me	75
$CH_2CH_2CH_2NEt_2$	Me	62

TABLE 6



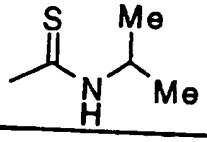
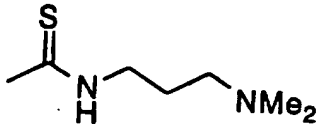
R5	% inhibition (50uM)
H	100
	96
	76

TABLE 7

Inhibition of NO Synthases by Cyclic Isothioureas

Example No.	iNOS IC_{50} (uM)	ecNNOS IC_{50} (uM)	ncNOS IC_{50} (uM)
1	0.018	0.065	0.029
12	3.03	> 50	< 0.5
13	1.43	12.4	0.3
14	16	> 50	ND
15	< 50	ND	ND
16	ND	ND	ND
19	13	50	9.6
20	12.2	> 50	5

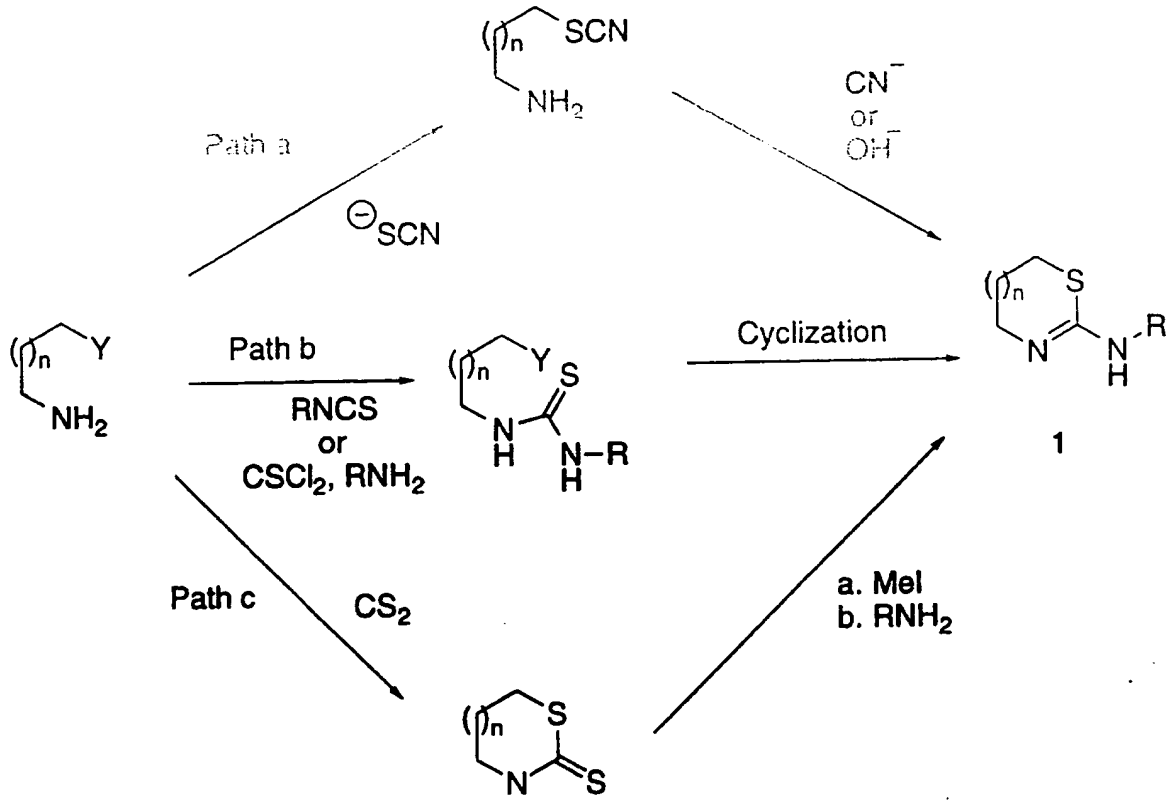
21	2.7	1.8	0.59
23	22	> 25	6.7
24	1.25	> 25	6.1
25	0.34	7.4	0.54
26	0.012	0.28	0.02
27	0.0045	0.34	0.023
28	0.169	40.5	4.85
29	0.028	1.4	0.252
30	0.0141	0.68	0.052
31	0.015	0.094	0.021
32	0.073	1.38	0.073
33	0.016	0.5	0.024
34	1.05	5.47	0.083
35	0.007	< 0.1	< 0.1
36	0.056	< 0.5	< 0.1
37	>50	>50	>50
38	0.66	2.5	0.1
39	0.019	< 0.1	< 0.1
40	0.33	1.8	0.1
41	21	24.3	1

Several methods for preparing the compounds of this invention are illustrated in the following schemes and examples. Some of the compounds are known in the literature. A limited number of substituted thiazole and thiazoline derivatives are reported to be inhibitors of NO synthase. See WO 94/12165 and J. Biol. Chem. 1994, 289, 26669-76. Unless otherwise stated, starting materials were obtained from commercial sources. In one method illustrated by example 1 (Scheme 1: path a), these compounds are prepared by reacting an aminoalkyl halide with potassium thiocyanate and the resulting aminoalkylthiocyanate is cyclized in the presence of a base or a cyanide ion. The aminoalkyl halides starting materials are commercially available or they can be prepared by the methods known to those skilled in the art. Alternatively the amine substrate for the displacement reaction may contain a different leaving group such as a mesylate or a tosylate which are prepared fron the corresponding alcohol using the methods described in March J. *Advanced Organic Chemistry*, 3rd ed., John Wiley & Sons, NewYork, p. 444 (1985).

In an alternative method of synthesis as shown in scheme 1: path b, and illustrated by example 2, the amine is first reacted with an acylating agent such as an alkyl, aryl or acyl isothiocyanate and the resulting thiourea is cyclized upon heating with or without a base catalyst. If an acylisothiocyanate is used (Example 19) a 2-acylaminothiazine product is obtained.

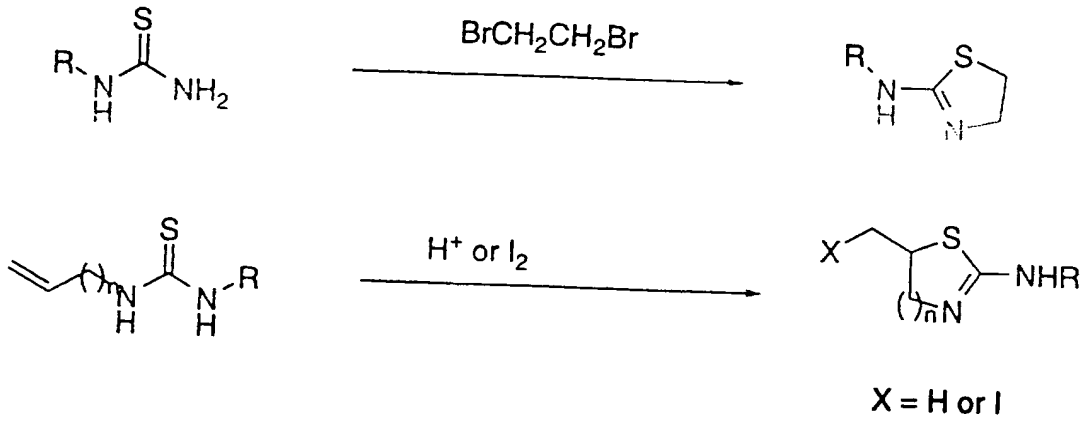
Path c of scheme 1 shows a third way for forming the desired ring structures. In this method the aminoalcohol, halide or other suitable derivative is reacted with carbon disulfide to form the heterocyclic ring system with a thiocarbonyl group. Methylation and displacement of the resulting methylthio group with ammonia or an amine gives the desired 2-amino substituted heterocycle.

SCHEME 1



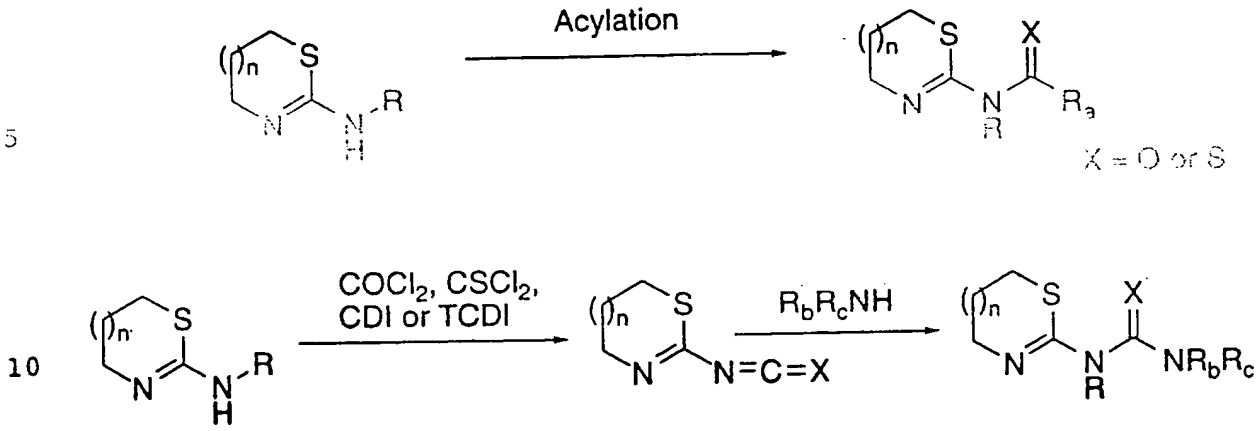
Two methods for the preparation of cyclic compounds from a thiourea are shown in shceme 2 and illustrated by examples 21 and 22. Thus reaction of a thiourea with 1,2-dibromoethane can give a thiazoline (Example 21). Alternatively if the thiourea contains a double bond, cyclization in the presence of an acid can result in the desired ring. Alternatively iodocyclization (Example 22) can lead to an iodo derivative which can be further modified by hydrolysis or by displacement reactions as shown in examples 23 and 24.

SCHEME 2



The 2-aminothiazoline (and other rings) prepared by methods shown in schemes 1 or 2 can be further modified, for example by acylation (scheme 3). Thus reaction of 2-Amino-5,6-dihydro-4H-1,3-thiazine with an acid chloride or anhydride optionally in the presence of a base gives a 2-acylamino analog. Other acylation procedures as described in March J., Advanced Organic Chemistry, 3rd ed., John Wiley & Sons, New York, (1985) may also be used. If an isocyanate or an isothiocyanate (Example 12) is used for acylation, the product is a urea or a thiourea. Alternatively ureas or a thioureas can also be prepared by reacting the amino compound with phosgene, thiophosgene, or other carbonyl tranfer reagents such as carbonyldiimidazole or thiocarbonyldiimidazole followed by reaction with another amine (Example 15) .

SCHEME 3



The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature of up to 60°C; the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only; melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations; the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data; yields are given for illustration only; when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 400 MHz or 500 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal; chemical symbols have their usual meanings; the

following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

The preparation and biological properties of isothioureas have been reported in the literature (Schroeder, *Chem, Revs.*, 1955, *55*, 181; Doherty *et al.*, *J. Am. Chem. Soc.*, 1957, *79*, 5667; and Brand and Brand, *Org. Synth.*, 1942, *22*, 59; Smirk *et al.*, Brit. Med. J., 1941, 510-11; J. Physiol., 1942, *100*, 474-483; Lancet, 1942, 301-303; J Physiol., 1943, *101*, 379-388; Fastier, Brit. J. Pharmacol., 1948, *3*, 198).

EXAMPLE 1

2-Amino-5,6-dihydro-4H-1,3-thiazine.

A flask containing 8.76 g (40 mmol) of 3-bromopropylamine hydrobromide and 3.89 g (40 mmol) of potassium thiocyanate in 25 mL of water was heated in a 100 °C bath. After heating overnight most of the water had evaporated. The reaction was cooled and the remaining volatiles were removed in vacuo. The residue was treated with 100 mL of hot absolute EtOH, the undissolved solid (KBr) was filtered. Upon cooling the filtrate white crystals were formed. The crystals were were filtered, washed with cold EtOH and dried to obtain 6.2 g of solid. In a 1 lit 3- neck flask equipped with an addition funnel and a gas outlet tube, containing 2.05 g (31.5 mmol) of KCN in 500 mL of water a solution of 6.2 g of the solid obtained above in 125 mL of water was dropwise added. After stirring the reaction mixture overnight, it was acidified by adding 48% HBr. Since HCN gas may be produced during this operation the escaping gases were passed through a trap of 5N NaOH. The resulting yellow solution was heated in a 40 oC bath for 4 h, then 4 g of activated charcoal was added and the mixture was kept stirred at 40 oC for 2 h more. The reaction was filtered through a pad of celite and the filtrate was concentrated. The remaining water in the residue was removed by adding MeOH and concentration. The residual solid was treated with 60 mL of MeOH and filtered to remove KBr. The filtrated

was reduced to about 20 mL and allowed to cool to RT. The solution was diluted with EtOAc (50 mL) and on standing crystals were formed. The solid was filtered, washed with EtOAc and dried to isolate 3.2 g of the title compound. An additional 0.97 g (53% total) of thtitle compound was obtained from the filtrate by concentration and cooling.

^{1}H NMR ($CDCl_3$) δ: 1.79 (m, 2 H), 3.0 (m, 2 H), 3.48 (m, 2 H).
Mass Spectrum m/e = 117 (M+1).

EXAMPLE 2

2-Methylamino-5,6-dihydro-4H-1,3-thiazine.

A mixture of 0.19 g (0.87 mmol) of 3-bromopropylamine hydrobromide in 3 mL of toluene containing 63 uL (0.92 mmol) of methylisothiocyanate and 0.16 uL (0.92 mmol) of diisopropylethylamine was heated to reflux. After 30 min the starting hydrobromide had dissolved and a yellow oil separated. The reaction mixture was cooled and extraced with water. The combined aqueous extract was washed with ether. The water layer was made basic (pH = 10) by adding 2N NaOH and then extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine and dried over Na_2SO_4 and the filtrate was concentrated to provide 68 mg (60 %) of the title compound.

^{1}H NMR ($CDCl_3$) δ: 1.80 (m, 2 H), 2.77 (s, 3 H), 3.0 (m, 2 H), 3.54 (m, 2 H).

Mass Spectrum m/e = 131(M+1).

Compounds of Examples 3- 11 were prepared by following the procedure of Example 2 by substituting an appropriate isothiocyanate for methylisothiocyanate.

EXAMPLE 3

2-Ethylamino-5,6-dihydro-4H-1,3-thiazine.

^{1}H NMR ($CDCl_3$) δ: 1.11 (t, 3 H), 1.80 (m, 2 H), 3.0 (t, 2 H, J = 6 Hz), 3.20 (q, 2 H, J = 7 Hz), 3.52 (m, 2 H).
Mass Spectrum m/e = 145(M+1).

EXAMPLE 4

2-Propylamino-5,6-dihydro-4H-1,3-thiazine.
Mass Spectrum m/e = 159(M+1).

EXAMPLE 5

2-(2-Methylethyl)amino-5,6-dihydro-4H-1,3-thiazine.
Mass Spectrum m/e = 159(M+1).

EXAMPLE 6

2-Butylamino-5,6-dihydro-4H-1,3-thiazine.
Mass Spectrum m/e = 173(M+1).

EXAMPLE 7

2-(2,2-Dimethylethyl)amino-5,6-dihydro-4H-1,3-thiazine.
Mass Spectrum m/e = 173(M+1).

EXAMPLE 8

2-(Cyclohexyl)amino-5,6-dihydro-4H-1,3-thiazine.
Mass Spectrum m/e = 199(M+1).

EXAMPLE 9

2-Phenylamino-5,6-dihydro-4H-1,3-thiazine.

EXAMPLE 10

2-(3-Dimethylaminpropyl)amino-5,6-dihydro-4H-1,3-thiazine.
Mass Spectrum m/e = 202(M+1).

EXAMPLE 11

2-(2-Dimethylaminoethyl)amino-5,6-dihydro-4H-1,3-thiazine.

^{1}H NMR (CD3OD) δ: 2.24 (m, 2 H), 3.31 (s, 6 H), 3.31 (m, 2 H), 3.62 (t, 2 H), 3.71 (t, 2 H), 3.88 (t, 2 H).

EXAMPLE 12

2-(3-Diethylaminopropylamino-thiocarbonyl-amino)-5,6-dihydro-4H-1,3-thiazine.

To a solution of 80 mg (0.615 mmol) of 3-diethylaminopropylamine in 1 mL of $CHCl_3$ and 1 mL of saturated $NaHCO_3$ was added 47 uL (0.615 mmol) of thiophosgene. After vigorously stirring the mixture for 0.5 h, the layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried and concentrated. The residue was dissolved in 1 mL of DMF and the solution was added to 0.1 g (0.512 mmol) of 2-amino-5,6-dihydro-4H-1,3-thiazine hydrobromide in 1 mL of DMF and 86 uL (0.615 mmol) of Et_3N. The mixture was heated at 60 °C for 4 h, then allowed to cool to room temperature over night. The reaction was partitioned between water and EtOAc. The EtOAc layer was washed with water, brine, dried and the filtrate was concentrated. The residue was purified by prep TLC using 30 % MeOH-EtOAc to isolate 48 mg (33 %) of the title compound.
Mass Spectrum m/e = 289, 196, 173, 157,125, 100.

EXAMPLE 13

2-(3-Dimethylaminopropylamino-thiocarbonyl-amino)-5,6-dihydro-4H-1,3-thiazine.

^{1}H NMR ($CDCl_3$) δ:1.64 (m, 2 H), 1.78 (m, 2 H), 2.17 (s, 6 H), 2.31 (t, 2 H, J = 7 Hz), 3.0 (m, 2 H), 3.25 (t, 2 H, J = 7 Hz), 3.52 (m, 2 H).

Mass Spectrum m/e = 261, 216, 186, 173, 159.

EXAMPLE 14

2-(2-Dimethylaminoethylamino-thiocarbonyl-amino)-5,6-dihydro-4H-1,3-thiazine.

By substituting 2-dimethylaminoethylamine for 3-diethylaminopropylamine in example 12 the title compound was obtained.

Mass Spectrum m/e = 247, 213, 202, 159.

EXAMPLE 15

2-(3-Diethylaminopropyl)methylamino-thiocarbonyl-amino)-5,6-dihydro-4H-1,3-thiazine.

A solution of 74 mg (0.38 mmol) of 2-amino-5,6-dihydro-3H-1,3-thiazine hydrobromide in 2 mL of DMF was treated with 63 uL (0.45 mmol) of Et_3N and 67 mg (0.38 mmol) of 1,1'-thiocarbonyldiimidazole. After stirring for 1 h, 66 mg (0.45 mmol) of N,N-diethyl-N'-methyl-1,3-propanediamine was added and the mixture was heated to 50 °C. After 2 h the reaction was cooled and partitioned between water and EtOAc. The aqueous layer was extraced with EtOAc and each EtOAc layer was washed with water, brine, dried, combined and concentrated. The residue was purified by prep TLC using 30 % MeOH-EtOAc to isolate 39 mg (34 %) of the title compound.

Mass Spectrum m/e = 303, 170, 145, 125.

The compounds of examples 16-18 were prepared by the procedure of example 15 and substituting the appropriate diamine for N,N-diethyl-N'-methyl-1,3-propanediamine.

EXAMPLE 16

2-(2-Dimethylaminoethyl)ethylamino-thiocarbonyl-amino)-5,6-dihydro-4H-1,3-thiazine.

Mass Spectrum m/e = 275,159,145, 142, 129, 117.

EXAMPLE 17

2-(2-Diethylaminoethyl)ethylamino-thiocarbonyl-amino)-5,6-dihydro-4H-1,3-thiazine.

Mass Spectrum m/e = 303, 170, 159, 145, 143, 118, 102(M+1).

EXAMPLE 18

2-(2-Dimethylaminoethyl)phenylmethylamino-thiocarbonyl-amino)-5,6-dihydro-3H-1,3-thiazine.

Mass Spectrum m/e = 337, 292, 207, 191, 177, 159.

EXAMPLE 19

2-Benzoylamino-4H-3,1-benzothiazine

Step A: 1-(2-Bromomethyl)phenyl-3-benzoyl-thiourea.

To a solution of 0.223 g (1.81 mmol) of 2-aminobenzyl alcohol in 7 mL of toluene was added 0.24 mL (1.81 mmol) of benzoyl isothiocayante. After stirring the mixture under N_2 atmosphere for 2 h, the reaction was partitioned between water and EtOAc. The water layer was extracted with EtOAc and each EtOAc layer was washed with brine, dried, combined and concentrated to obtain 0.449 g of a residue. A solution of this residue in 8 mL of MeCN was added to a solution of

dibromotriphenylphosphorane prepared by adding bromine to 0.53 g (2 mmol) of triphenylphosphine in 4 mL of MeCN. After stirring the reaction for 1 h the solution was diluted with EtOAc, washed with water, brine, dried and concentrated. The residue was chromatographed on a flash column using 20% EtOAc-Hexane to furnish 0.16 g (27%) of the title compound.

^{1}H NMR (CDCl3) δ: 4.03 (s, 2 H), 7.1-7.6 (m, 7 H), 8.2 (d, 2 H, J = 7 Hz).

Step B: 2-Benzoylamino-4H-3,1-benzothiazine.

A solution of 0.158 g (0.45 mmol) of 1-(2-bromomethyl)phenyl-3-benzoyl-thiourea (from step A) in 2 mL of toluene containing 0.13 mL (0.9 mmol) of Et_3N was heated to reflux. After 4 h the solution was cooled, diluted with EtOAc, washed with water, brine, dried and concentrated. The residue was purified by prep TLC using 50% EtOAc-hexane to isolate 0.107 g (88%) of the title compound.

^{1}H NMR ($CDCl_3$) δ:4.01 (s, 2 H), 7.0-7.5 (m, 7 H), 8.16 (d, 2 H, J = 7 Hz).

Mass Spectrum m/e = 269(M+1).

EXAMPLE 20

2-Amino-4H-3,1-benzothiazine

A suspension of 98 mg (0.37 mmol) of 2-benzoylamino-4H-3,1-benzothiazine (Example 19) in 4 mL of 2 N HCl was heated to reflux. After 24 h at reflux the solution was cooled and washed with CH_2Cl_2. The aqueous layer was concentrated to isolate 39 mg (52%) of the title compound as a yellow solid.

^1H NMR (CD_3OD) δ: 4.27 (s, 2 H), 7.15-7.6 (m, 4 H).
Mass Spectrum m/e = 165(M+1).

EXAMPLE 21

5-(2-Thiazolinyl)amino-norvaline hydrochloride.

Step A: N^a-(t-Butoxycarbonyl)-5-(2-thiazolinyl)amino-norvaline t-butyl ester.

A solution of 0.118 g (0.33 mmol) of N^a-(t-butoxycarbonyl)-5-thioureido-norvaline t-butyl ester (Tet. Lett. 1991, 32, 875-878) in 2 mL of CH_2Cl_2 was treated with 86 uL (1 mmol) of 1,2-dibromoethane and 0.175 mL (1 mmol) of diisopropylethylamine. The vial was tightly capped and heated in a 40 °C bath overnight. The solution was diluted with CH_2Cl_2, washed with water, brine, dried and concentrated. The residue was chromatographed on a flash column using a gradient of EtOAc to 80:19:1 EtOAc:MeOH:Et_3N to isolate 54 mg (44%) of the title compound.

^1H NMR ($CDCl_3$) δ: 1.42 (s, 9 H), 1.44 (s, 9 H), 1.5-1.9 (m, 4 H), 3.17 (t, 2 H, J = 7 Hz), 3.45 (q, 2 H, J = 7 Hz), 3.64 (t, 2 H, J = 7 Hz), 4.1 (m, 1 H), 5.28 (m, 1 H).

Step B: 5-(2-Thiazolinyl)amino-norvaline hydrochloride.

HCl gas was passed through 2 mL EtOAc at 0 °C until it was saturated. This solution (2 mL) was added to 54 mg (0.144 mmol) of Nα-(t-butoxycarbonyl)-5-(2-thiazolinyl)amino-norvaline t-butyl ester (from step A) and the mixture was stirred overnight. A white solid was formed. The mixture was diluted with Et_2O, the solid was filtered, washed with Et_2O and dried to obtain 46 mg (quantitative) of the title compound.

^1H NMR (CD_3OD) δ: 1.75-2.1 (m, 4 H), 3. 55 (t, 2 H, J = 7 Hz), 3.62 (t, 2H, J = 7 Hz), 4.06 (t, 1 H, J = 7 Hz), 4.12 (t, 2 H, J = 7 Hz).

EXAMPLE 22

5-(S)-2-Imino-3-thia-1-aza-bicyclo(3.3.0)octane.

Step A: 5-(S)-2-Thioxo-3-thia-1-aza-bicyclo(3.3.0)octane.

To a solution of 2.5 g (24.5 mmol) of 2-(S)-pyrrolidinomethanol in 10 mL of dry chloroform at 0 °C was bubbled hydrogen chloride gas until saturation. After 10 min. at 0 °C, 3.6 mL (49.4 mmol) of thionyl chloride was introduced and the mixture was refluxed for 90 min. Reaction mixture was cooled to room temperature and stirred overnight (approximately 15 h). Excess thionyl chloride and chloroform were removed under vacuum . The black residue was treated with methanol and successive treatment with charcoal, filteration and concentration furnished 2.3 g of a light yellow hygroscopic solid which was used in the next step.

To a solution of 1.58 g (10 mmol) of 2-(S)-chloromethyl-pyrrolidine (from the above) in 10 mL of dry methylene chloride under nitrogen at 0 °C was added 1.0 ml (15 mmol) of CS_2 followed by 4.2 mL (45 mmol) of triethylamine. The reaction mixture was warmed to the room temperature stirred for 3 hours, at which point CS_2 and triethylamine were removed under vacuum. The residue was taken up in water and filtered. The solid was repeatedly washed with water and was then dried giving 1.5g (82% yield) of the title compound as a yellowish white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.59 (m, 1H), 3.59 (dd, 1H), 3.43(dd, 1H), 3.29 (m, 2H), 2.20-2.42 (m, 1H), 2.18 (m, 1H), 1.74 (m, 1H).

[illegible] 35.79, 31.35, 28.79.

Step B: 5-(S)-2-Imino-3-thia-1-aza-bicyclo(3.3.0)octane.

To a solution of 1 g (6.28 mmol) of 5-(S)-2-Thioxo-3-thia-1-aza-bicyclo(3.3.0)octane in 5 ml of dimethoxyethane at room temperature was added 0.78 ml (12. 4 mmol) of iodomethane and stirred at room temperature for 3 hours. Evaporation of the solvent and excess iodomethane gave the solid residue which was washed with ether giving 1.64 g (99% yield) of a solid.

^{1}H NMR (500 MHz, D_2O) δ 5.11 (m, 1H), 3.83 (dd, 1H), 3.65-3.71 (m, 2H), 2.85 (s, 3H), 2.47-2.60 (m, 2H), 2.32-2.37 (m,2H), 2.00 (m, 1H).
^{13}C NMR (400 MHZ, D_2O) δ 186.70, 77.23, 48.12, 36.87, 29.26, 28.96, 18.10.

Ammonia gas was passed through a solution of 0.303 g (1 mmol) of the solid obatined above in 5 ml of dry methanol at room temperature for 15 min.. The reaction was allowed to proceed overnight (15 hrs). Evaporation of methanol in vacuum gave the title compound.

^{1}H NMR (500 MHz, D_2O) δ 4.73 (m, 1H), 3.44-3.56 (m, 4H), 2.37-2.47 (m, 2H), 2.18 (m, 1H), 1.81(m, 1H).
^{13}C NMR (400 MHz, D_2O) δ 70.78, 44.99, 35.01, 29.69, 28.89.

EXAMPLE 23

2-Amino-4-iodomethyl-thiazoline

Anhydrous ammonia was passed through a solution of 1.5 g (15.1 mmol) of allyl isothiocyanate in 30 mL of methanol for 20 min. After stirring for 3 h the reaction was complete, so the mixture was concentrated and the residue was chromatographed using 10:10:1 hexane/EtOAc/MeOH to isolate 1.13 g (64%) of allylthiourea.

To a solution of 1.0 g of allylthiourea in 10 mL of CH_2Cl_2 2.5 g (9.67 mmol) of iodine was added. Within 1 h a pale yellow precipitate appeared. After 3 h all the starting material was consumed, the solid was filtered. The filtrate was washed with 10 % $NaHSO_3$ solution, brine and concentrated to give additional solid which was combined with the yellow solid and washed with chloroform and dried to furnish 1.73 g (74%) of the title compound.

^1H NMR (500 MHz, DMSO) δ 9.3 (br s, 2H), 4.35 (m, 1H), 3.95 (q, 1H), 3.71 (dd, 1H), 3.59 (m, 1H)..
^{13}C NMR (500 MHz, DMSO) δ 151, 54, 49,10.

EXAMPLE 24

2-Amino-4-hydroxymethyl-thiazoline

To a mixture of 100 mg (0.413 mmol) of 2-amino-4-iodomethyl-thiazoline (from Example 23) in 2.5 mL of nitromethane and 1.5 mL of water was added 137 mg (0.617 mmol) of silver trifluoroacetate. The mixture was vigorously stirred overnight and the next morning it was filtered through celite. Concentration of the filtrate gave 42 mg (76%) of the title compound as a grey solid.

^1H NMR (500 MHz, DMSO) δ 10 (s, 1H), 9.35 (s, 2H), 4.08 (m, 1H), 3.88 (dd, 1H), 3.75 (dd, 1H), 3.53 (m, 1H).
^{13}C NMR (500 MHz, DMSO) δ 172.5, 63, 50.5, 50.

EXAMPLE 25

S-((2-amino-thiazolino)methyl)isothiourea

To a mixture of 350 mg (1.45 mmol) of 2-amino-4-iodomethyl-thiazoline (from Example 23) in 3 mL of dioxane were added 473 mg (2.17 mmol) of di-t-butyldicarbonate and 3 mL of saturated NaHCO3. The reaction was stirred overnight, filtered and the filtrate was [illegible] hexane/EtOAc to obtain 330 mg (69%) of 2-t-butoxycarbonylamino-4-iodomethyl-thiazoline.

^{1}H NMR (500 MHz, CDCl3) δ 4.21 (dd, 1H), 4.05 (m, 1H), 3.73 (m, 1H), 3.4 (dd, 1H), 3.3 (t, 1H), 1.55 (s, 9H).

To a solution of 120 mg (0.35 mmol) of 2-t-butoxycarbonylamino-4-iodomethyl-thiazoline in 4 mL of absolute EtOH was added 32 mg (0.425 mmol) of thiourea and the solution was stirred overnight. The precipitated solid was filtered and washed with cold EtOH, dried to furnish 20 mg of S-((2-t-butoxycarbonylamino-thiazolino)methyl)isothiourea.

^{1}H NMR (500 MHz, CDCl3) δ 4.0 (m, 2H), 3.85 (br s, 1H), 3.45 (br s, 1H), 3.3 (br s, 1H), 1.55 (s, 9H).

To a solution of 12 mg of S-((2-t-butoxycarbonylamino-thiazolino)methyl)isothiourea in 3 mL of EtOAc, HCl gas was bubbled to saturate it. After stirring the solution overnight the solvent was evaporated and the residual solid was washed with chloroform to furnish 5.1 mg of the title compound.
^{1}H NMR (500 MHz, CD3OD) δ 4.4 (br s, 1H), 4.05 (br s), 3.9 (br s, 1H) 3.6 (br s, 1H).
^{13}C NMR (500 MHz, CD3OD) δ 172, 54, 49.6.

EXAMPLE 26

2-Amino-cis-5,6-dimethyl-5,6-dihydro-4H-1,3-thiazine, methanesulfonic acid salt

Step A: 2-Methyl-3-hydroxy-butyronitrile

To a solution of 0.97 mL of [illegible] 30 mL of THF 2.1 g (20 mmol) of LiCN.THF was added and the mixture was heated to reflux [illegible] and extracted with Et_2O. The Et_2O solution was washed with water, brine dried and concentrated to yield 0.392 g of the title compound sufficiently pure for use in the next step.

Step B: 4-t-Butyloxycarbonylamino-3-methyl-2-butanol

A solution of 0.892 g (9 mmol) of 2-methyl-3-hydroxy-butyronitrile in 30 mL of Et_2O was treated with 0.683 g (18 mmol) of LiAlH4 and the resulting was heated to reflux for 2 h. The reaction mixture was cooled in an ice bath and 0.68 mL of water, 0.68 mL of 15% NaOH and 2.04 mL of water were added. The solution was stirred for 0.5 h whereby the aluminium salts coagulated. The solution was filtered through a pad of Na_2SO_4 and the pad was rinsed with more Et_2O. The combined filtrate was concentrated leaving a yellow oil. The oil was dissolved in 10 mL of acetonitrile and 10 mL of 1N NaOH followed by 2.166 g (9.926 mmol) of di-t-butyldicarbonate were added. After stirring for 3 h the reaction mixture was partitioned between water and EtOAc. The organic layer was washed with brine, dried and concentrated. The residue was chromatographed using 30-50% EtOAc-hexane to yield 0.92 g of the title compound.

Step C: 3-Methanesulfonyloxy-2-methyl-butylamine hydrochloride.

A solution of 0.323 g (1.773 mmol) of 4-t-butyloxycarbonylamino-3-methyl-2-butanol in 8 mL of CH_2Cl_2 was treated with 0.15 mL (1.95 mmol) of methanesulfonyl chloride and O.3 mL (2.128 mmol) of Et3N at O °C. After 10 min the ice bath was removed and the solution was allowed to warm to room temperature over the next 1 h. The reaction was partitioned between water and CH_2Cl_2 and the aqueous layer was extraced with CH_2Cl_2. The combined organic

layer was washed with brine, dried and concentrated. The residue was dissolved in 15 mL of EtOAc saturated with HCl gas. After stirring for 3 h the solution was concentrated leaving 0.455 g of the title compound.

Step C: 2-Amino-cis-5,6-dimethyl-5,6-dihydro-4H-1,3-thiazine.

To a well stirred solution of 0.455 g (2.09 mmol) of 3-methanesulfonyloxy-2-methyl-butylamine hydrochloride in 5 mL of $CHCl_3$ and 5 mL of saturated $NaHCO_3$, 0.18 mL (2.3 mmol) of thiophosgene was added. After 50 miin the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried and concentrated. The residue was purified rapidly on a flash column using 30% EtOAc-hexane to furnish 92 mg of the isothiocyanate. This product was dissolved in 6 mL of MeOH which was previously saturated with NH3 and the reaction was stirred overnight. The solution was concentrated leaving 81 mg of the title compound.

^1H NMR (CD_3OD) δ: 1.07 (d, 3 H), 1.37 (d, 3H), 2.38 (m, 1H), 2.69 (s, 3H), 3.34 (dd, 1H), 3.48 (dd, 1H), 3.72 (qd, 1H, J=7 and 3.2 Hz).

Mass Spectrum m/e = 145(M+1).

EXAMPLE 27

2-Amino-trans-5,6-dimethyl-5,6-dihydro-4H-1,3-thiazine hydrobromide

To a solution of 0.402 g (2.2 mmol) of 4-t-butyloxycarbonylamino-3-methyl-2-butanol (from Example 26, step B) in 10 mL of dry acetonitrile was added 1.12 g (2.65 mmol) of dibromotriphenylphosphorane. After stirring for 2 h the reaction mixture was quenched with water, the layers were separated and the aqueous layer was washed with EtOAc. The aqueous layer was concentrated and the residue was dissolved in 2 mL of $CHCl_3$ and 2 mL of saturated

$NaHCO_3$ and 0.095 mL (1.25 mmol) of thiophosgene was added. After stirring for 0.5 h the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried and concentrated. The residue was purified by prep TLC eluting with 30% EtOAc-hexane to isolate 33 mg of the desired product. A mixture was stirred for 6 h. The solution was concentrated leaving 23 mg of the desired product.

^1H NMR (CD_3OD) δ: 1.12 (d, 3 H), 1.41 (d, 3H), 1.95 (m, 1H), 3.17 (dd, 1H), 3.53 (dd, 1H), 3.37 (quintet, 1H, J=7 Hz).

Mass Spectrum m/e = 145 (M+1).

EXAMPLE 28

3-Amino-2-thia-4-aza-cis-bicyclo(4,4,0)-dec-3-ene hydrochloride (L-771,599)

The title compound was prepared from cyclohexaneoxide by the procedure of example 26.

^1H NMR (CD_3OD) δ: 1.1- 2.0 (m, 8 H), 2.3 (m, 1H), 3.45 (d, 2H), 3.95 (q, 1H, J=4 Hz).

Mass Spectrum m/e = 171 (M+1).

EXAMPLE 29

3-Amino-2-thia-4-aza-cis-bicyclo(4,3,0)-non-3-ene, methane sulfonic acid salt (L-771,598)

The title compound was prepared from cyclopentaneoxide by the procedure of example 26.

^{1}H NMR (CD_3OD) δ: 1.5- 2.0 (m, 6 H), 2.24 (m, 1H), 2.69 (s, 3H), 3.26 (dd, 1H), 3.48 (dd, 1H), 3.83 (q, 1H, J=6 Hz).

Mass Spectrum: m/e = 137 (M+1).

2-Amino-trans-4,5-dimethyl-5,6-dihydro-4H-1,3-thiazine

Step B: 3-Amino-2-methyl-1-butanol

A solution of 1.737 g (25 mmol) of hydroxylamine hydrochloride in 20 mL of MeOH was neutralized by adding 12.5 mL of 2N NaOH solution and 1.4 mL (10 mmol) of ethyl 2-methylacetoacetate was added. The mixture was stirred for 1 h and concentrated. The residue was dissolved in water and extracted with EtOAc. The EtOAc solution was washed with brine, dried and concentrated to give 0.974 g of a residue which was dissolved in 20 mL of Et_2O. The solution was cooled in an ice bath and 0.48 g of LiAlH4 was added. The suspension was heated to reflux for 2 h then cooled in ice bath and quenched by sequencially adding 0.48 mL of water, 0.48 mL of 15% NaOH solution and 1.5 mL of water. The mixture was stirred for 0.5 h to allow the aluminium salts to coagulate. The solution was filtered through Na_2SO_4 and the solid was rinsed with Et_2O. The combined filtrate was concentrated to yield 0.54 g of the title product as an oil which was used in the next step without purification.

Step B: 3-t-Butyloxyamino-2-methyl-1-butanol

A solution of 0.54 g of 3-amino-2-methyl-1-butanol in 6 mL of acetonitrile and 6 mL of 1N NaOH was treated with 1.371 g () of dit-butyldicarbonate. After stirring overnight the reaction mixture was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc. The combined EtOAc layer was washed with brine, dried and concentrated. The resdue was chromatographed on a flash column

using a gradient of 20-30% EtOAc-hexane to isolate 0.26 g of the erythro (faster moving) isomer and 0.14 g of the threo (slower) isomer.

[illegible] 2-Amino-trans-4-[illegible]-5,6-dihydro-4H-1,3-thiazine, methane sulfonic acid salt

[illegible] prepared from the threo isomer of 3-t-butyloxyamino-2-methyl-1-butanol by the method described in Example 26 steps C and D.

^{1}H NMR (CD_3OD) δ: 1.15 (d, 3 H), 1.33 (d, 3H), 1.98 (m, 1H), 2.7 (s, 3H), 3.02 (dd, 1H), 3.21 (dd, 1H), 3.38 (quintet, 1H, J=7 Hz).

Mass Spectrum m/e = 145 (M+1).

EXAMPLE 31

2-Amino-cis-4,5-dimethyl-5,6-dihydro-4H-1,3-thiazine, methane sulfonic acid salt

The title compound was synthesized from erythro 3-t-butyloxyamino-2-methyl-1-butanol (Example 30, step B) according to the procedure of Example 26 steps C and D.

^{1}H NMR (CD_3OD) δ: 1.08 (d, 3 H), 1.24 (d, 3H), 2.33 (m, 1H), 2.7 (s, 3H), 3.06 (dd, 1H), 3.27 (dd, 1H), 3.72 (qd, 1H, J=6.8 and 3.4 Hz).

Mass Spectrum m/e = 145 (M+1).

EXAMPLE 32

4-Amino-3-thia-5-aza-trans-bicyclo(4,4,0)-dec-4-ene, methane sulfonic acid salt(L-773,191)

Step A: trans-1-Amino-2-hydroxymethyl-cyclohexane hydrochloride

The title compound was prepared fron ethyl cyclohexanone-2-carboxylate by the method described in Example 31 step A.

[illegible] sulfonic acid salt

[illegible] hydroxymethyl-cyclohexane hydrochloride by the procedure of Example 26 steps C and D.

^{1}H NMR (CD_3OD) δ: 1.1-2.1 (m, 9 H), 2.7 (s, 3H), 3.02 (m, 2H), 3.18 (m, 1H).

Mass Spectrum m/e = 171 (M+1).

EXAMPLE 33

1(S)-6(R)-4-Amino-3-thia-5-aza-cis-bicyclo(4.4.0)-dec-4-ene hydrochloride (L-770,425)

The title compound was prepared from 1(R)-2(S)-1-amino-2-hydroxymethyl-cyclohexane by the method of Example 26 steps C and D.

^{1}H NMR (CD_3OD) δ: 1.4-1.9 (m, 8 H), 2.32 (m,1H), 3.14 (dd, 1H), 3.33 (dd, 1H), 3.72 (m, 1H).

Mass Spectrum m/e = 171 (M+1).

EXAMPLE 34

1(R)-6(S)-4-Amino-3-thia-5-aza-cis-bicyclo(4.4.0)-dec-4-ene (L-766,423)

The title compound was prepared from 1(S)-2(R)-1-amino-2-hydroxymethyl-cyclohexane by the method of Example 26 steps C and D.

The compounds of Examples 35-38 were synthesized by the method of Example 25 using Cyanogen Bromide with the appropriate aminoalcohol

^{1}H NMR (CD_3OD) δ: 1.3-2.0 (m, 9 H), 2.85 (dd, 1H), 3.12 (dd, 1H)

Mass Spectrum m/e = 171 (M+1)

EXAMPLE 35

2-Amino-4-methyl-5,6-dihydro-4H-1,3-thiazine hydrochloride

^{1}H NMR (CD_3OD) δ: 1.32 (d, 3H), 1.83 (m, 1H), 2.3 (m, 1H), 3.25 (m, 2H), 3.7 (m, 1H).

Mass Spectrum m/e = 131 (M+1).

EXAMPLE 36

2-Amino-4-phenyl-5,6-dihydro-4H-1,3-thiazine hydrochloride

^{1}H NMR (CD_3OD) δ: 2.2-2.5 (m, 2H), 3.1 (m, 1H), 3.34 (m, 1H), 4.86 (dd, 1H), 7.3-7.5 (m, 5H).

Mass Spectrum m/e = 193 (M+1).

EXAMPLE 37

2-Amino-5-phenyl-5,6-dihydro-4H-1,3-thiazine hydrochloride

^{1}H NMR (CD_3OD) δ: 2.9-3.6 (m, 5H), 7.2-7.5 (m, 5H).

Mass Spectrum m/e = 193 (M+1).

EXAMPLE 38

2-Amino-5-methyl-5,6-dihydro-4H-1,3-thiazine hydrochloride

Mass Spectrum m/e = 131 (M+1).

EXAMPLE 39

[illegible]

^{1}H NMR (CD_3OD) δ: 1.43 (d, 3H), 1.82 (m, 1H), 2.3 (m, 1H), 3.45 (m, 2H), 3.65 (m, 2H).

Mass Spectrum m/e = 131 (M+1).

EXAMPLE 40

2-Amino-6,6-dimethyl-5,6-dihydro-4H-1,3-thiazine hydrochloride

^{1}H NMR (CD_3OD) δ: 1.52 (s, 6H), 2.06 (dd, 2H), 3.62 (dd, 2H).

Mass Spectrum m/e = 131 (M+1).

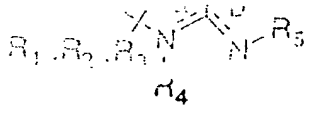
EXAMPLE 41

2-Amino-6-phenyl-5,6-dihydro-4H-1,3-thiazine hydrochloride

Mass Spectrum m/e = 193 (M+1).

WHAT IS CLAIMED IS:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof wherein:
side a or side b has a double bond,
n is 0, 1, 2, 3 or 4
X is selected from O, S and NH,
R_1, R_2 and R_3 are each independently selected from the group consisting of

(a) hydrogen,
(b) C1-12alkoxy,
(c) C1-12alkylS(O)k wherein k is 0, 1 or 2,
(d) mono C1-12alkylamino,
(e) (di-C1-12alkyl)amino,
(f) C1-12alkylcarbonyl,
(g) C1-12alkyl,
(h) C2-12alkenyl,
(i) C2-12alkynyl,
(j) C5-10cycloalkyl,
(k) hetero C5-10cycloalkyl,wherein the hetero C5-10cycloalkyl optionally contains 1 or 2 heteroatoms selected from S, O and N,
(l) aryl, selected from phenyl or naphthyl,
(m) heteroaryl, wherein heteroaryl is selected from the group consisting of:

(1) benzimidazolyl,

(2) benzofuranyl,
(3) benzooxazolyl,
(4) furanyl
(5) imidazolyl,
(6) indolyl,
(8) isothiazolyl,
(9) naphthyridinyl,
(10) oxazolyl,
(11) pyrazinyl,
(12) pyrazolyl,
(13) pyridyl,
(14) pyrimidyl,
(15) pyrrolyl,
(17) isoquinolyl,
(18) tetrazolyl,
(19) thiadiazolyl,
(20) thiazolyl,
(21) thienyl, and
(22) triazolyl,

(n) amino,
(o) oxo,
(p) C(O)OH,
(q) C(O)OR6, R6 is selected from hydrogen, phenyl, cyclohexyl or C1-6alkyl,

each of (b) to (m) being optionally mono or di- substituted the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) -NR6R7, where R7 is selected from hydrogen, phenyl, cyclohexyl or C1-6alkyl,
(4) -OR6,
(5) -CO2R6,
(6) -S(O)kR6,

(7) halo selected from F, Cl, Br and I,
(8) -C(=NR6)-NHR7,
(9) -S-C(=NR6)-NHR7,

[illegible] is hydroxy, amino, mono C1-4alkylamino or (di-C1-4alkylamino, said R1 [illegible]

[illegible]

or when two members of the group R1, R2 and R3 reside on the same carbon atom of Formula I, or two of the group R1, R2 and R3 reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the carbon atom to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R1, R2 and R3 resides on an atom adjacent to the N on which R4 resides, said member may optionally be joined with R4, such that together with the N on which R4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

R4 and R5 are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C1-12alkyl, optionally mono or di-substituted, the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) -NR6R7,
(4) -OR6,
(5) -CO2R6,
(6) -S(O)kR6,

(7) halo selected from F, Cl, Br and I,
(8) phenyl, optionally mono or di-substituted with
hydroxy, halo, C_{1-6}alkyl or C_{1-6}alkoxy,
(c) -CONR8R9, wherein R8 and R9 are each independently hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl, said C_{1-6}alkyl
(1) hydroxy,
(2) [illegible],
(3) carboxy,
(4) $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently H, C_{1-6}alkyl, phenyl or benzyl,
(5) $-OR_{10}$,
(6) $-CO_2R_{10}$,
(7) $-S(O)_mR_{10}$, where m is 0, 1 or 2,
(8) halo selected from F, Cl, Br and I,
(9) optionally substituted aryl wherein aryl and aryl substituents are as defined above,
(10) optionally substituted heteroaryl wherein heteroaryl and heteroaryl substituents are as defined above,
(11) optionally substituted C5-10cycloalkyl wherein cycloalkyl and cycloalkyl substituents are as defined above,
(12) optionally substituted hetero C_{5-10}cycloalkyl wherein hetero cycloalkyl and hetero cycloalkyl substituents are as defined above,
(d) -CSNR8R9,
(e) $-COR_9$,
(f) $-CO_2R_9$,
(g) $-CSR_9$,
(h) phenyl,
(i) cyclohexyl,

provided that R4 is present only when side a is a single bond and side b is a double bond, and further provided that when n is 0 or 1, X is S and R_1, R_2, R_3, and R_4 are hydrogen, then R_5 is other than hydrogen or methyl.

2. A compound according to claim 1 wherein

n is 0, 1, 2, 3 or 4;

Y is independently selected from the group consisting of:

R1, R2 and R3 are each independently selected from the group consisting of:

(a) hydrogen,

(b) C1-6alkoxy,

(c) C1-6alkylamino,

(d) C1-6alkylcarbonyl,

(e) C1-6alkyl,

(f) C2-6alkenyl,

(g) C2-6alkynyl,

(h) C5, C6 or C7cycloalkyl,

(i) hetero C5, C6 or C7cycloalkyl,wherein the hetero C5, C6 or C7cycloalkyl optionally contains 1 or 2 heteroatoms selected from S, O and N,

(j) aryl, selected from phenyl or naphthyl,

(k) heteroaryl, wherein heteroaryl is selected from the group consisting of:

(1) benzimidazolyl,
(2) benzofuranyl,
(3) benzooxazolyl,
(4) furanyl,
(5) imidazolyl,
(6) indolyl,
(7) isooxazolyl,
(8) isothiazolyl,
(9) oxadiazolyl,
(10) oxazolyl,
(11) pyrazinyl,
(12) pyrazolyl,
(13) pyridyl,
(14) pyrimidyl,

(15) pyrrolyl,
(16) quinolyl,
(17) tetrazolyl,
(18) thiadiazolyl,
(19) thiazolyl,

(20) thienyl,

the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) -NR6R7, where R6 and R7 are selected from hydrogen, phenyl, cyclohexyl or C1-6alkyl,
(4) -OR6,
(5) -CO2R6,
(6) -S(O)kR6,
(7) halo selected from F, Cl, Br and I,
(8) -C(=NR6)-NHR7,
(9)-S-C(=NR6)-NHR7,

or when two members of the group R1, R2 and R3 reside on the same carbon atom of Formula I, or two of the group R1, R2 and R3 reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the carbon atom to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R1, R2 and R3 resides on an atom adjacent to the N on which R4 resides, said member may optionally be joined with R4, such that together with the N on which R4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle

optionally containing up to three hetero atoms selected from N, O or S,

R4 and R5 are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-6}alkyl, optionally [illegible]

[illegible]

(2) carboxy,

(3) -NR_6R_7,

(4) -OR_6,

(5) -$CO2R_6$,

(6) -$S(O)_kR_6$, where k is 0, 1 or 2,

(7) halo selected from F, Cl, Br and I,

(c) -$CONR_8R_9$, where R_8 and R_9 are each independently hydrogen, phenyl, cyclohexyl or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) -$NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently H, C_{1-4}alkyl, phenyl or benzyl,

(5) -OR_{10},

(6) -$CO2R_{10}$,

(7) -$S(O)_mR_{10}$, where m is 0, 1 or 2,

(8) halo selected from F, Cl, Br and I,

(9) optionally substituted aryl wherein aryl andaryl substituents are as defined above,

(10) optionally substituted heteroaryl wherein heteroaryl and heteroaryl substituents are as defined above,

(11) optionally substituted C_5, C_6 or C_7cycloalkyl wherein cycloalkyl and cycloalkyl substituents are as defined above,

(12) optionally substituted hetero C5, C6 or C7cycloalkyl wherein hetero cycloalkyl and hetero cycloalkyl substituents are as defined above,

(d) -CSNR8R9,

(e) -COR9,

(g) -CSR9,

(h) phenyl,

(i) cyclohexyl,

such that R4 is present only when side a is a single bond and side b is a double bond.

3. A compound according to claim 2 wherein

n is 0, 1, 2, 3 or 4,

X is selected from O, S and NH,

R1, R2 and R3 are each independently selected from the group consisting of

(a) hydrogen,

(b) C1-6alkoxy,

(c) C1-6alkylamino,

(d) C1-6alkylcarbonyl,

(e) C1-6alkyl,

(f) C2-6alkenyl,

(g) C5, C6 or C7cycloalkyl,

(h) hetero C5 or C6 cycloalkyl,wherein the hetero C5 or C6 cycloalkyl optionally contains 1 heteroatom selected from S, O and N,

(i) aryl, selected from phenyl or naphthyl,

(j) heteroaryl, wherein heteroaryl is selected from the group consisting of:

(1) furanyl,

(2) pyrazinyl,

(3) pyrazolyl,

(4) pyridyl,

(5) pyrimidyl,
(6) thiazolyl,
(7) [illegible]yl, and
(8) [illegible]azolyl,

each of (b) to (i) being optionally [illegible] selected from

(1) hydroxy,

(2) [illegible],

(3) -NR6R7, wherein R6 and R7 are each independently hydrogen or C1-4alkyl,

(4) -OR6,

(5) -CO2R6,

(6) -S(O)kR6, where k is 0, 1 or 2,

(7) halo selected from F, Cl, Br and I,

(8) -C(=NR6)-NHR7,

(9)-S-C(=NR6)-NHR7,

or when two members of the group R1, R2 and R3 reside on the same carbon atom of Formula I, or two of the group R1, R2 and R3 reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the carbon atom to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R1, R2 and R3 resides on an atom adjacent to the N on which R4 resides, said member may optionally be joined with R4, such that together with the N on which R4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

R4 and R5 are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-6}alkyl, optionally mono or di-substituted, the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(4) -OR6,
(6) -S(O)kR6,
(7) halo selected from F, Cl, Br and I,

(c) -CONR8R9, where R8 and R9 are each independently hydrogen, phenyl, cyclohexyl or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by
(1) hydroxy,
(2) amino,
(3) carboxy,
(4) -NR10R11, wherein R10 and R11 are each independently H, C_{1-4}alkyl, phenyl or benzyl,
(5) -OR10,
(6) -CO2R10,
(7) -S(O)mR10, where m is 1 or 2,
(8) halo selected from F, Cl, Br and I,
(9) optionally substituted aryl wherein aryl and aryl substituents are as defined above,
(10) optionally substituted heteroaryl wherein heteroaryl and heteroaryl substituents are as defined above,
(11) optionally substituted C_5 or C_6 cycloalkyl wherein cycloalkyl and cycloalkyl substituents are as defined above,
(12) optionally substituted hetero C_5 or C_6 cycloalkyl wherein hetero cycloalkyl and hetero cycloalkyl substituents are as defined above,

(d) -CSNR8R9,

(e) -COR9,

(f) $-CO_2R_9$,
(g) $-CSR_9$,
(h) phenyl,
(i) cyclohexyl,

such that R_4 is present only when side a is a single bond

[illegible] according to Claim 3 wherein

n is 0, 1, 2 or 3,

X is selected from O, S and NH,

R_1, R_2 and R_3 are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-4}alkoxy,
(c) C_{1-4}alkylamino,
(d) C_{1-4}alkylcarbonyl,
(e) linear and branched C_{1-4}alkyl,

each of (b) to (e) being optionally mono or di- substituted the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,
(4) $-OR_6$,
(5) $-CO_2R_6$,
(6) $-S(O)_kR_6$, where k is 0, 1 or 2,
(7) halo selected from F, Cl, Br and I,

or when two members of the group R_1, R_2 and R_3 reside on the same carbon atom of Formula I, or two of the group R_1, R_2 and R_3 reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the carbon atom to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms,

said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R1, R2 and R3 resides on an atom adjacent to the N on which R4 resides, said member may optionally be joined with R4, such that together with the N

resides there is formed a saturated or unsaturated

optionally containing up to three hetero atoms selected from N, O or S,

R4 and R5 are each independently selected from the group consisting of

(a) hydrogen,

(b) -CONR8R9, where R8 and R9 are each independently hydrogen or C1-3alkyl, said C1-3alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) -NR10R11, wherein R10 and R11 are each independently H or C1-3alkyl,

(5) -OR10,

(6) -CO2R10,

(7) -S(O)mR10, where m is 0, 1 or 2,

(8) halo selected from F, Cl, Br and I,

(c) -CSNR8R9,

(d) -COR9,

(e) -CO2R9,

(f) -CSR9,

(g) -C1-4alkyl.

5. A compound according to Claim 4 wherein

n is 0, 1, 2 or 3

X is selected from O, S and NH,

R_1, R_2 and R_3 are each independently selected from the group consisting of

(a) hydrogen,

(b) C_{1-4}alkoxy,

(c) C_{1-4}alkylamino,

(e) linear and branched C_{1-4}alkyl, optionally mono or di- substituted the substituents being independently selected from

(1) hydroxy,

(2) carboxy,

(3) $-NR_6R_7$, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,

(4) $-OR_6$,

(5) $-CO_2R_6$,

(6) $-S(O)_kR_6$, where k is 0, 1 or 2,

(7) halo selected from F, Cl, Br and I,

R_4 is selected from the group consisting of

(a) hydrogen,

(b) $-CONHR_9$, where R_9 is hydrogen or C_{1-3}alkyl, said C_{1-3}alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently C_{1-3}alkyl,

(5) $-OR_{10}$,

(6) $-CO_2R_{10}$,

(7) $-S(O)_mR_{10}$, where m is 1 or 2,

(8) halo selected from F, Cl, Br and I,

(c) $-CSNHR_9$;

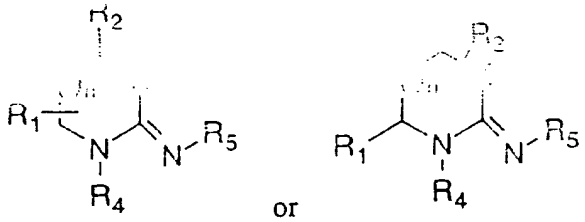
(d) $-C_{1-4}$alkyl.

R_5 is selected from the group consisting of

(a) hydrogen,

(b) -CONHR9,
(c) -CSNR8R9.
(d) -C1-4alkyl.

5 A compound according to Claim 4 of the formula



or

or tautomers thereof wherein
n is 0, 1 or 2.

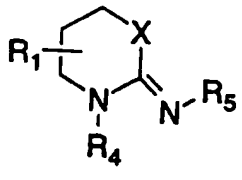
7. A compound according to Claim 6 wherein
n is 0, 1 or 2,
X is selected from O, S and NH,
R1 and R2 are each independently selected from the group consisting of
(a) hydrogen,
(b) linear and branched C1-4alkyl,
each of (a) and (b) being optionally mono or di- substituted
the substituents being independently selected from
(1) carboxy,
(2) -NHR7, wherein R6 and R7 are each independently hydrogen or C1-3alkyl,
(3) -OR6,
(4) -CO2R6,
(5) -S(O)kR6, where k is 0, 1 or 2,
R4 is selected from the group consisting of
(a) hydrogen,
(b) -CONHR9, where R9 is hydrogen or C1-3alkyl, said C1-3alkyl optionally substituted by
(1) hydroxy,
(2) amino,

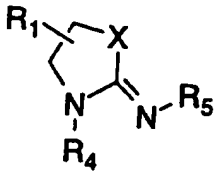
(3) carboxy,
(4) -$NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently
C_{1-3}alkyl,
(5) -OR_{10},
(7) -$S(O)_mR_{10}$, where m is 0, 1 or 2,

(c) -CSNHR9;
(d) C_{1-3}alkyl;

R_5 are each independently selected from the group consisting of
(a) hydrogen,
(b) -CONHR9,
(c) -CSNR8R9,
(d) C_{1-3}alkyl.

8. A compound according to Claim 7 of the formulae



or


9. A compound according to Claim 8 wherein
X is selected from S and NH,
R_1 is selected from the group consisting of
(a) hydrogen,
(b) linear and branched C_{1-4}alkyl, said C_{1-4}alkyl being optionally mono or di- substituted the substituents being independently selected from
(1) carboxy,
(2) -NR_6R_7, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,
(3) -OR_6,

(4) -CO2R6,

(5) -S(O)kR6, where k is 0, 1 or 2,

R4 is selected from the group consisting of

(a) hydrogen,

(b) -CONHR9, where R9 is hydrogen or C1-4alkyl, said C1

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) -NR10R11, wherein R10 and R11 are each independently

C1-3alkyl,

(5) -OR10,

(6) -CO2R10,

(7) -S(O)mR10, where m is 0, 1 or 2,

(8) halo selected from F, Cl, Br and I,

(c) -CSNHR9;

(d) C1-3alkyl;

R5 is selected from the group consisting of

(a) hydrogen,

(b) -CONHR9,

(c) -CSNR8R9,

(d) C1-3alkyl.

10. Acompound according to Claim 9 wherein

X is selected from S and NH,

R1 is selected from the group consisting of

(a) hydrogen,

(b) linear and branched C1-4alkyl, said C1-4alkyl being optionally mono or di- substituted the substituents being independently selected from

(1) carboxy,

(2) -NHR7, wherein R6 and R7 are each independently hydrogen or C1-3alkyl,

(3) -CO2R6, and

(4) -S(O)kR6, where k is 0, 1 or 2,

R4 is selected from the group consisting of

(a) hydrogen,

(b) C1-3alkyl,

(a) hydrogen,

(b) [illegible] hydrogen or C1-4alkyl, said

C1-4alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) -NR10R11, wherein R10 and R11 are each independently

C1-3alkyl,

(5) -OR10,

(6) -CO2R10,

(7) -SR10, and

(8) -S(O)mR10, where m is 1 or 2,

(9) halo selected from F, Cl, Br and I,

(c) -CSNR8R9,

(d) C1-3alkyl.

11. A compound of Claim 1 selected from

(a) 2-Amino-5,6-dihydro-3H-1,3-thiazine;

(b) 2-Methylamino-5,6-dihydro-3H-1,3-thiazine;

(c) 2-Ethylamino-5,6-dihydro-3H-1,3-thiazine;

(d) 2-Propylamino-5,6-dihydro-3H-1,3-thiazine;

(e) 2-(2-Methylethyl)amino-5,6-dihydro-3H-1,3-thiazine;

(f) 2-Butylamino-5,6-dihydro-3H-1,3-thiazine;

(g) 2-(2,2-Dimethylethyl)amino-5,6-dihydro-3H-1,3-thiazine;

(h) 2-(Cyclohexyl)amino-5,6-dihydro-3H-1,3-thiazine;

(i) 2-Phenylamino-5,6-dihydro-3H-1,3-thiazine;

(j) 2-(3-Dimethylaminpropyl)amino-5,6-dihydro-3H-1,3-thiazine;

(k) 2-(2-Dimethylaminoethyl)amino-5,6-dihydro-3H-1,3-thiazine;

(l) [illegible]

(m) [illegible]

(n) 2-(2-Dimethylaminoethylamino-thiocarbonyl-amino)-5,6-dihydro-3H-1,3-thiazine;

(o) 2-(3-Diethylaminopropyl)ethylamino-thiocarbonyl-amino)-5,6-dihydro-3H-1,3-thiazine;

(p) 2-(2-Dimethylaminoethyl)propylamino-thiocarbonyl-amino)-5,6-dihydro-3H-1,3-thiazine;

(q) 2-(2-Diethylaminoethyl)propylamino-thiocarbonyl-amino)-5,6-dihydro-3H-1,3-thiazine;

(r) dihydro-3H-1,3-thiazine;

(s) 2-Benzoylamino-4H-3,1-benzothiazine;

(t) 2-Amino-4H-3,1-benzothiazine;

(u) 5-(2-Thiazolinyl)amino-norvaline hydrochloride;

(v) 5-(S)-2-Imino-3-thia-1-aza-bicyclo(3.3.0)octane;

(w) 2-Amino-4-iodomethyl-thiazoline;

(x) 2-Amino-4-hydroxymethyl-thiazoline; and

(y) S-((2-amino-thiazolino)methyl)isothiourea, or a pharmaceutically acceptable salt thereof.

12. A compound according to Claim 1 selected from the group consisting of

(a) 2-Amino-cis-5,6-dimethyl-5,6-dihydro-4H-1,3-thiazine, methanesulfonic acid salt,

(b) 2-Amino-trans-5,6-dimethyl-5,6-dihydro-4H-1,3-thiazine hydrobromide,

(c) 3-Amino-2-thia-4-aza-cis-bicyclo(4,4,0)-dec-3-ene hydrochloride,

(d) 3-Amino-2-thia-4-aza-cis-bicyclo(4,3,0)-non-3-ene, methane sulfonic acid salt,

(e) 2-Amino-trans-4,5-dimethyl-5,6-dihydro-4H-1,3-thiazine,

(f) [illegible]

(g) [illegible]

(h) 1(S)-6(R)-4-Amino-3-thia-5-aza-cis-bicyclo(4,4,0)-dec-4-ene hydrochloride,

(i) 1(R)-6(S)-4-Amino-3-thia-5-aza-cis-bicyclo(4,4,0)-dec-4-ene,

(j) 2-Amino-4-methyl-5,6-dihydro-4H-1,3-thiazine hydrochloride,

(k) 2-Amino-4-phenyl-5,6-dihydro-4H-1,3-thiazine hydrochloride,

(l) 2-Amino-5-phenyl-5,6-dihydro-4H-1,3-thiazine hydrochloride,

(m) 2-Amino-5-methyl-5,6-dihydro-4H-1,3-thiazine hydrochloride,

(n) 2-Amino-6-methyl-5,6-dihydro-4H-1,3-thiazine hydrochloride,

(m) 2-Amino-6,6-dimethyl-5,6-dihydro-4H-1,3-thiazine hydrochloride, and

(n) Amino-6-phenyl-5,6-dihydro-4H-1,3-thiazine hydrochloride.

13. A pharmaceutical composition for treating a nitric oxide synthase mediated disease comprising a pharmaceutical carrier and a non-toxic effective amount of the compound of Claim 1.

14. A method for inhibiting the activity of nitric oxide synthases comprising administering to a subject suffering from a nitric

oxide synthase mediated disease, a non-toxic therapeutically effective amount of the compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14512

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/211, 227.2, 227.5, 227.8, 358, 369, 370, 371, 376, 377, 395, 397; 540/544; 544/54, 55; 548/146, 181, 190, 193, 225, 233, 234, 251, 240, 304.7, 311.1, 326.5, 328.1, 330.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, Volume 116, issued 1992, Mazurek et al., "Theoretical studies on tautomerism of clonidine in vacuum and in water medium", page 773, second column, abstract 58395n, THEOCHEM, 82(1-2), pages 23-28, see entire abstract.	1-12
X	WO, A, 94/12165 (THE WELLCOME FOUNDATION LIMITED) 09 June 1994, pages 4-18 and formula (I) on page 4.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
20 FEBRUARY 1996

Date of mailing of the international search report
04 MAR 1996

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
Y.N. GUPTA
Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14512

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-14 (in part)

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14512

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/33, 31/415, 31/42, 31/425, 31/54, 31/55; C07D 235/04, 233/02, 233/44, 263/04, 263/28, 277/04, 277/18, 279/06, 267/06, 281/02

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/211, 227.2, 227.5, 227.8, 358, 369, 370, 371, 376, 377, 395, 397; 540/544; 544/54, 55; 548/146, 181, 190, 193, 225, 233, 234, 251, 240, 304.7, 311.1, 326.5, 328.1, 330.1

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

GROUP II, Claims 1-14, drawn to compounds, composition and method of use, when in formula I, n is zero and the substituents in R's are pyridyl or isopropyl.

GROUP III, Claims 1-14, drawn to compounds, composition and method of use, when in formula I, n is zero and the substituents in R's are pyrazinyl or pyrimidinyl.

GROUP IV, Claims 1-14, drawn to compounds, composition and method of use, when in formula I, n is one and X is -O-.

GROUP V, Claims 1-14, drawn to compounds, composition and method of use, when in formula I, n is one and X is -S- .

GROUP VI, Claims 1-14, drawn to compounds, composition and method of use,when in formula I, n is one and X is -NH- .

GROUP VII, Claims 1-14, drawn to compounds, composition and method of use, when in formula I, n is two and X is -O- or -S- .

GROUP VIII, Claims 1-14, drawn to compounds, composition and method of use, when in formula I, n is two and X is -NH- .

GROUP IX, Claims 1-14, drawn to compounds, composition and method of use, when in formula I, n is three or four and X is -O-, -S- or -NH- .

The invention of Groups I - IX, are made independently and are used independently. They are independent.

The inventions of Groups I - IX, are drawn to structurally dissimilar compounds and they are so diverse that if, thiazoles, oxazoles and diazoles of Group I, were anticipated, applicants would not acquiesce in objection of any of Groups I-IX there over or vice-versa. Accordingly, the claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept.